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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/998,832	11/29/2001	Robert Chow	020035-001100US	7166

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EXAMINER	
SHUKLA, RAM R	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 11/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/998,832	CHOW ET AL.	
	Examiner	Art Unit	
	Ram R. Shukla	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 August 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-9,11-13 and 15-27* is/are pending in the application.

4a) Of the above claim(s) *3-9 and 11-13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 15-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's response and amendment filed 08/19/04 has been received and entered.

2. Claims 2, 10 and 14 have been cancelled.

3. Claims 3-9, 11-13 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper filed 10-20-2003.

4. This application contains claims 3-9, 11-13 drawn to an invention nonelected with traverse in Paper filed 10-20-2003. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

5. Claims 1, 15-27 drawn to a method of preventing or treating HIV infection by screening for stem cells that have a beneficial gene that alters the ability of HIV to infect cells and transplanting said cells into a patient, wherein said beneficial gene encodes a receptor or co-receptor for HIV entry, wherein said receptor is CCR5 claims are under consideration.

6. It is noted that due to an inadvertent error, the statement of the statutory basis of the enablement rejection was not present in the previous office action. The paragraph is now added. This is not a new rejection.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1, 15-27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement for reasons of record set forth in the previous office action of 2/13/04 and reiterated below. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)).

Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

Claimed invention encompasses a method of preventing or treating HIV infection by first screening of plurality of cells of any origin for stem cells that have a beneficial gene and then transplanting these cells into a patient thereby preventing or treating HIV infection. Dependent claims limit the beneficial gene to a polymorphism of proteins expressed in immune cells and that the protein is a receptor or co-receptor for HIV entry in a cell, the co-receptor being CCR5 and the polymorphism being deletion of a 32 base pair region in the coding region or the promoter region of CCR5. Other claims recite that the stem cells are typed for HLA by certain method and the stem cells are screened by a certain method and that the stem cells are treated to express a non-native HLA protein or to inhibit expression of native HLA protein.

The specification as filed does not provide sufficient guidance to isolate the cells and use them in treating or preventing HIV infection in a patient and an artisan of skill would have required undue experimentation to practice the claimed invention because the art of HIV prevention or treatment was unpredictable at the time of the invention and neither the art of record nor the specification provide guidance to practice the claimed method as discussed below.

The specification as filed discusses the state of the art that the known HIV resistance genes are polymorhic form of CCR5 and CXCR4 coreceptors and of SDF1 promoter, RANTES

promoter, IL-10 promoter. The specification also states that HLA alleles also influence HIV-1 disease progression (see pages 1-2 of the specification). The specification also states on page 3:

> **[09]** The discovery that certain polymorphisms confer resistance to HIV has led to the proposal of therapies which repopulate the immune system with cells more capable of resisting infection and/or more capable of neutralizing the virus. By preventing *de novo* infection of cells, such therapy can eliminate the need for prolonged treatment with inhibitors of viral replication. Furthermore, the specific nature of such therapies should reduce side effects.

This clearly indicates that at the time of the filing of the instant application, the treatment with certain polymorphisms that conferred resistance to HIV was a hypothesis and the art of record did not teach how to treat or prevent HIV infection using these polymorphisms.

Rest of the specification is a disclosure of general molecular biology methods and techniques, but there is no specific guidance for treating HIV infection in a patient as recited in the claims. Figure 1 is flow chart, again of general steps, without any specifics. The methodology for transplantation of stem cell rich cell population into patients and therapeutic applications has been described in two paragraphs each, again comprising general statements and lacking any specific information. In summary, the specification does not provide any specific teaching for practicing the claimed method and does not teach any working examples for treatment or prevention of HIV in patients. It is noted that the specification neither teaches any working example in an animal model nor it teaches method for treating human patients.

At the time of the invention, as discussed in the specification, the art reported correlation of HIV co-receptor CCR5 polymorphism in HIV infected patients with disease progression (eg. see McDermott et al. The Lancet 352:866-870, 1998; Roman et al. HIV Clin. Trials 3: 195-201, 2002), however, the art of record did not teach how to treat or prevent HIV infection in a patient by transplanting stem cells that have the protective polymorphism. In fact there were contradictory reports in certain instances where the CCR5 polymorphism did not provide protection, rather it caused acceleration of disease (see last paragraph in the right column on page 195 continued on page 196). Therefore, at the time of the invention there was no evidence of treating or preventing HIV infection in a patient by transplanting stem cells with any beneficial gene polymorphism and treatment of a HIV infection or prevention of HIV infection would have been unpredictable since a number of factors played role in the process of blocking infection

(see the last paragraph in the left column of page 1317 and the specification does not teach as to how these auxiliary factors or other polymorphic proteins would have been provided to a patient. Claims 11-15 list CD4, CCR2, CCR2-641 and CCR5, however, the art does not provide sufficient teachings as to what polymorphisms would make a patient HIV infection resistant or treat HIV infection. In fact it has been reported that polymorphism in the promoter region of CCR5 increases HIV infectivity. Stephen O'brien and Michael Dean in review in Scientific American (September 1997), proposed destroying all HIV infected blood cells in a patient and then rescuing the patient with the bone marrow from donors who are homozygous for the deletion mutant of CCR5 and they discussed the limitations of the method and the finding that some individuals homozygous for CCR5 mutant got infected with HIV and predicted that any preventives or therapies aimed at blocking HIV's access to CCR5 could backfire and encourage, instead of forestall, infection and advancement to AIDS (see 50 and 51). This clearly establishes the unpredictability of the method of treatment of HIV infection or HIV infection prevention and the specification does not add to cure these deficiencies by providing any teachings for practicing the claimed method. The specification does not provide any guidance as to how would an artisan decide which polymorphism will be beneficial. Additionally, specification does not teach what polymorphism of CD4 would be beneficial since CD4 is the most common and efficient HIV infection in a T lymphocyte.

It is noted that while the specification discusses the known polymorphisms reported in the art, it does not provide how would an artisan screen for any other beneficial gene or what parameters will describe a beneficial gene or how would an artisan isolate a stem cell that has a beneficial gene with a certain polymorphism other than the polymorphism of certain genes reported in the art. The specification does not provide any guidance regarding the characteristics of the mutation or polymorphism that could be used for identifying a beneficial gene and screen a stem cell that expressed the beneficial gene. The specification on page 10 describes a general method of hybridization and immunological methods, but does not provide any specific guidance regarding the characteristics of probe to be used in the hybridization or immunological method. The specification does not provide any specifics or determinants as to what will be considered a beneficial gene. It is noted that at the time of the invention while the art taught to screen for PBMC, CD3+ cells, CD4+ lymphocytes and CD4+ monocytes or other blood types for the expression of a gene, the art did not teach how to screen for a stem cell from which all differentiated cells would have a certain polymorphism. For example, earlier studies in

the art (see Shieh et al. International Immunology 12: 1311-1318, 2000, page 1313, first full paragraph in the right column) indicated that only a certain percent of PBMCs expressed surface CCR5 and there was decreased average protein quantity in individuals heterozygous for CCR5delat32. Neither the art nor the specification teaches what amount of a beneficial gene comprising stem cell will be required to treat or prevent HIV infection.

The specification does not teach how to isolate the stem cells with a beneficial gene and expand them ex vivo or in vivo in an amount sufficient for transplantation. At the time of the invention, ex vivo expansion of hematopoietic stem and progenitor cells in general was unpredictable (see the entire article by Srour et al. The Journal of Hematotherapy 8:93-102, 1999, particularly page 97) and it was not routine in the art to in vivo expand stem cells for transplantation in patients. Since in the instant case the stem cells will have a particular mutation in a receptor or co-receptor gene, it would be unpredictable what kind of culture conditions would be required to expand and maintain the stem cells in vitro. It is noted that while the art teaches that CCR5 delta 32 mutant may make a cell resistant to HIV infection, it does not provide any guidance for culturing and maintaining a stem cell expressing the mutant CCRE5 or any other beneficial gene and it is unpredictable whether such a stem cell would be viable in vitro and what would be the role of a mutant gene in the survival of the cell in vivo or ex vivo.

The specification does not provide any guidance regarding the patient in which the stem cells be transplanted, for example, what would be the state of the endogenous stem cells that would be already infected with HIV or that would be susceptible to HIV infection because if the patient still has the infected cells or the HIV infection susceptible cells, the patient will still be infected with HIV. The specification does not teach as to how will the endogenous stem cells and cells of a HIV infected patient or a patient will be depleted and will be prevented from repopulating the hematopoietic cells of a patient.

Claim 18 recites that the source of the cells for screening is umbilical cord blood. The specification does not teach how the cells will be screened from an umbilical cord blood sample, identified, isolated and expanded ex vivo or in vivo.

Therefore, in view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, one of ordinary skill in the art at the time of the invention would have required an undue amount of experimentation to screen stem cells with beneficial genes and transplant them in a patient to prevent or treat HIV infection. It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the

accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991).

Response to Arguments

Applicant's arguments filed 8/19/04 have been fully considered but they are not persuasive. Applicants amended claim 1 by inserting the phrases: "from a human donor" in step (a), "the human" in step (b), and "in a human" in the preamble. Accordingly, the enablement rejection pertaining to the issue of xenogeneic transplantation has been withdrawn. However, other issues of rejection remain and the applicants' arguments are not persuasive to address these issues. Applicants have argued that examiner has improperly focused on inoperative embodiments. However, these arguments are not persuasive because the enablement rejection was not based on the inoperative embodiments rather on what has been taught in the specification for practicing the claimed invention and what is known in the art and whether an artisan of skill could make and use the claimed invention without undue experimentation. In response to applicants' discussion of *In re Cook and Merigold 169 USPQ 302* and *Ex Parte Forman 230 USPQ 546*, it is noted that these case laws are not applicable in this case because, first, no embodiment is enabled in the instantly claimed invention and second, the enablement rejection was based on analysis according to In re Wands, as discussed in the MPEP. In contrast to applicants' arguments, Courts have stated, eg., "It is true, as Genentech argues, that a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement." (See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966))

Applicants have argued that bone marrow transplantation of stem cells for treatment of HIV are no different that bone marrow treatment of other disorders. In response, applicants' attention is drawn to specific issue of enablement related to stem cell transplantation and HIV

infection, unpredictability of stem cell transplantation and unpredictability of stem cell expansion ex vivo discussed in the office action (see pages 5-7 of the previous office action). All these issues are specific issues and Applicants neither addressed these issues nor they provided any factual evidence to support their arguments that the specification as filed was enabling for the claimed invention. Therefore, the rejection is maintained for reasons of record set forth in the previous office action of 2/13/2004.

The written description of claims 1 and 18-26 is withdrawn in view of applicants' amendment filed 8/19/04.

9. No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

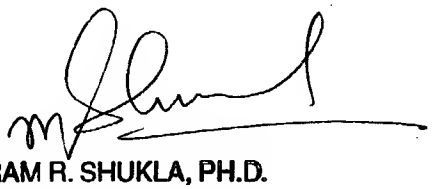
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (571) 272-0735 . The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached at (571) 272-0804. The fax phone number for TC 1600 is (703) 872-9306. Any inquiry of a general nature, formal matters or relating to the status of this application or

proceeding should be directed to the Dianiece Jacobs whose telephone number is (571) 272-0532.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ram R. Shukla, Ph.D.
Primary Examiner
Art Unit 1632



RAM R. SHUKLA, PH.D.
PRIMARY EXAMINER